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SYNTHESES OF ACYCLIC ANALOGUES OF KAINOIDS AND NEUROEXCITATORY ACTIVITY

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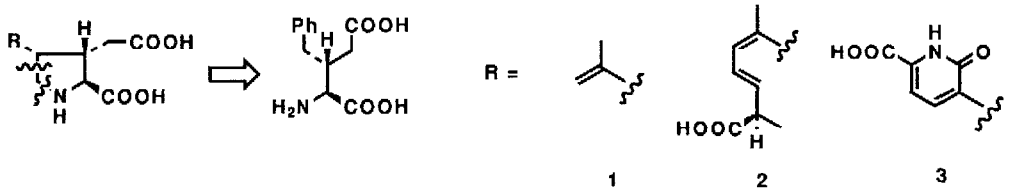
Summary: Four configurational isomers of 3-benzylglutamic acid, acyclic analogues of kainoids were synthesized to examine their structure-activity relationship.

Recently, several kainoids[1] such as kainic acid (**1**), domoic acid (**2**), and acromelic acid A (**3**)[2] have been widely available as useful tools in neuroscience research due to their extremely potent excitotoxic activity in the vertebrate and invertebrate glutamatergic system.[3] These kainoids cause a marked depolarization of the mammalian central neurones which lead to specific neuronal death in the brain. The pharmacological effects and patterns of neuronal degeneration observed after injection of kainoids have been extensively studied and shown to mimic the symptoms and alternations of neuronal pathways observed in patients suffering from neuronal diseases such as epilepsy and Huntington's chorea. In addition, there is a possibility that neuronal death caused by kainoids is a good experimental model for neuronal cell loss in the senile dementia. On the other hand, there are only a few experiments performed from the configurational aspect of kainoids, which are expected to provide useful information about elucidating the mechanism underlying the neuronal damage caused by excitatory amino acids.

The potent neuroexcitatory activity of kainic acid possibly depends on both the restricted conformation of the glutamate skeleton involved as a constitutional structure and a trigonal carbon atom attached to C_4 of the pyrrolidine ring.[4] Therefore, we are interested in the structure **10**, where

the pyrrolidine ring is cleaved to release the limited movement of the glutamate moiety and the configuration of the benzyl group placed at C-3 is the same as that of biologically active kainoids (Fig. 1). In the present paper, we describe the syntheses of acyclic kainoid analogues and their excitatory activity in the rat spinal cord in vitro.

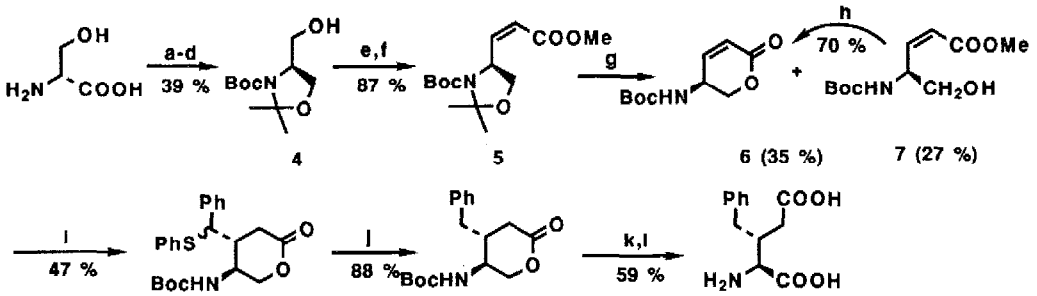
Fig. 1



1 2 3

Two isomers, (2S,3R)- and (2R,3S)-3-benzylglutamic acids (10 and its enantiomer) were obtained as follows. (4S)-N-t-Butoxycarbonyl-2,2-dimethyl-4-hydroxymethyl-1,3-oxazoline(4), prepared from D-serine in usual manner,[5] was oxidized to aldehyde which was converted into cis-α,β-unsaturated ester 5[6]. Treatment of 5 with CSA in MeOH yielded a mixture of unsaturated lactone 6[7] (35%) and deprotected alcohol 7 (27%). The by-product 7 could be converted into lactone with CSA in CH_2Cl_2. Introduction of a benzyl group to the lactone 6 was successfully carried out using a Michael addition of benzyl-phenylsulfide.

Scheme 1



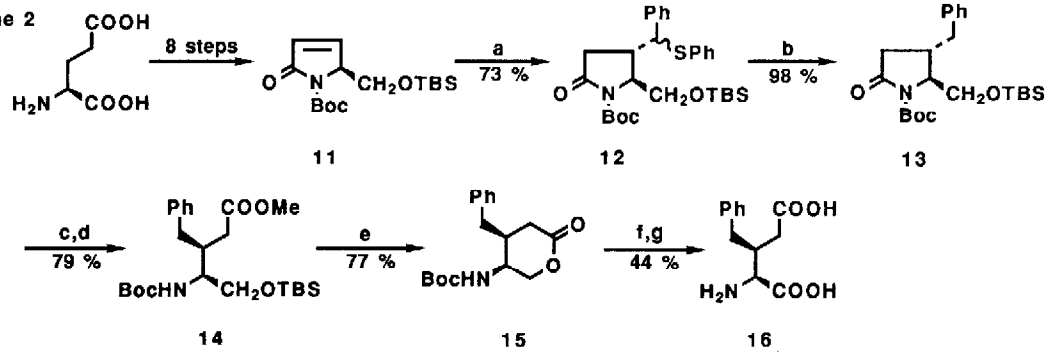
a) Boc-ON, Et_3N, 1,4-dioxane, H_2O b) CH_2N_2, MeOH c) 2,2-dimethoxypropane, CSA, acetone, d) $LiAlH_4$, Et_2O, 0 °C e) Swern ox., -78 °C f) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, KH, $(TMS)_2NH$, 18-crown-6, THF, -78 °C g) p-TsOH, MeOH h) p-TsOH, CH_2Cl_2 i) $PhCH_2SPh$, N,N,N',N'-tetramethylethylenediamine (TMEDA), n-BuLi, -78 °C j) n-Bu_3SnH, AIBN, benzene, reflux k) $KMnO_4$, 1M NaOH l) TFA

The reaction provided (4R,5S)-8 exclusively which was desulfurized with tributyltin hydride to give desired 9[7](88%). This was converted into (2S,3R)-3-benzylglutamic acid 10[7] by the following procedure: (1) $KMnO_4$, 1M

NaOH (2) TFA (2 steps 59%). Enantiomer of 10[7], (2R,3S)-10, was obtained from L-serine using the same procedure as above.

On the other hand, (2S,3S) and (2R,3R) isomers were synthesized from the known γ-lactam 11.[8] Treatment of the lactam 11 with PhCH(SPh)Li gave Michael adduct 12 (73%) which was desulfurized with Raney nickel(W-2) in acetone-water[9] to give 13[7](98%). This was converted into cis-substituted lactone 15[7] in 3 steps (1: hydrolysis of lactam, 2: esterification, 3: desilylation with HFaq.[10], 61% through 3 steps). Treatment of 15 in the same way as the preparation of 9 gave (2S,3S)-16[7](44%). Enantiomer of 16[7] was also synthesized from (2R)-11.

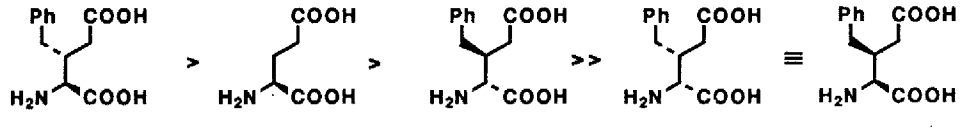
Scheme 2



a) $PhCH_2SPh$, TMEDA, n-BuLi, THF, -78 °C b) Raney nickel (W-2), acetone, H_2O, reflux c) 1M NaOH, MeOH d) CH_2N_2, MeOH e) HF_{aq}, CH_3CN f) $KMnO_4$, 1M NaOH g) TFA

(2S,3R)-3-Benzylglutamic acid (10), which had similar configuration to biologically active kainoids, demonstrated the most potent neuroexcitatory activity of the four isomers, and its depolarizing activity was three times as potent as that of L-glutamic acid. Its enantiomer, (2R,3S) isomer, was considerably less active than L-glutamic acid. On the other hand, (2S,3S) and (2R,3R) isomers had little activity. D-Glutamic acid derivatives demonstrated to be less active. Thus, the above results suggest that (2S,3R) configuration plays a key role for the neuroexcitatory action.

Relative potency ratio of synthetic glutamate analogues in the rat spinal cord



(2S,3R)		(2R,3S)	(2R,3R)	(2S,3S)
(3)	(1)	(0.3)	(<< 0.1)	(<< 0.1)

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7) **6**: $[\alpha]_D^{27}$ +99.7° (c 1.1, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ1.46 (s, 9H), 4.35-4.52 (3H), 4.78 (br s, 1H), 6.10 (dd, 1H, J= 1, 10 Hz) and 6.88 (dd, 1H, J= 5, 10); **9**: mp 92-95 °C; $[\alpha]_D^{25}$ -17.0° (c 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ1.45 (s, 9H), 2.16 (m, 1H), 2.27 (dd, 1H, J= 10, 16 Hz), 2.56 (dd, 1H, J= 6, 16), 3.84 (br s, 1H), 4.11 (br dd, 1H, J= 6, 12), 4.34 (dd, 1H, J= 4, 12), 4.63 (br d, 1H, J= 6) and 7.14-7.32 (5H); (2S,3R)-**10**: mp 155-157 °C; $[\alpha]_D^{25}$ +15.7° (c 0.2, H_2O); ^1H NMR (500 MHz, D_2O) δ 2.41 (dd, 1H, J= 6, 17 Hz), 2.47 (dd, 1H, J= 7, 17), 2.65 (dd, 1H, J= 10, 15), 2.72 (m, 1H), 2.86 (dd, 1H, J= 5, 15), 3.84 (d, 1H, J= 3) and 7.28-7.38 (5H); (2R,3S)-**10**: mp 156-158 °C; $[\alpha]_D^{21}$ -16.2°(c 0.2, H_2O); **13**: mp 44-46 °C; $[\alpha]_D^{25}$ -39.3° (c 1.0, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ0.01 (s, 6H), 0.85 (s, 9H), 1.53 (s, 9H), 2.17 (dd, 1H, J= 1, 18 Hz), 2.51-2.81 (3H), 2.83 (dd, 1H, J= 8, 18), 3.60 (dd, 1H, J= 8, 18), 3.82-3.89 (2H) and 7.14-7.36 (5H); **15**: mp 150-151 °C; $[\alpha]_D^{25}$ -24.4° (c 1.1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ1.48 (s, 9H), 2.32 (m, 1H), 2.42-2.49 (2H), 2.62 (dd, 1H, J= 6, 18 Hz), 2.84 (dd, 1H, J= 6, 14), 4.05 (br s, 1H), 4.32 (dd, 1H, J= 2, 12), 4.41 (dd, 1H, J= 2, 12), 4.85 (br s, 1H) and 7.14-7.36 (5H); (2S,3S)-**16**: mp 144-145 °C; $[\alpha]_D^{25}$ +30.8° (c 0.2, H_2O); ^1H NMR (500 MHz, D_2O) δ2.23 (d, 2H, J= 5 Hz), 2.58 (m, 1H), 2.77 (d, 2H, J= 8), 3.69 (d, 1H, J= 4) and 7.22-7.35 (5H); (2R,3R)-**16**: mp 144-146 °C; $[\alpha]_D^{22}$ -34.6° (c 0.2, H_2O)

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